AMENDMENTS TO THE SPECIFICATION

At the following points of the specification, delete "active" and insert therefore --reactive--:

Please replace paragraph [0001] at page 1 with the following amended paragraph:

[0001]

The present invention relates to a nanocolloidal platinum dispersion containing nanocolloidal platinum and a colloid-protecting agent, which has excellent ability to remove ~~active~~ reactive oxygen species, and its production method, and a drink containing such nanocolloidal platinum.

Please replace paragraph [0006] at page 2 with the following amended paragraph:

[0006]

When a human body takes a large amount of oxygen by vigorous sports or labor, he suffers from the generation of excess active oxygen species, and loses moisture and minerals by fatigue and perspiration, resulting in decrease in the activity of antioxidant enzymes and thus the accumulation of large amounts of ~~active~~ reactive oxygen species in the body. Having sports drinks, etc. containing minerals is effective to recover from fatigue by making up for the lost moisture and minerals. However, because conventional sports drinks do not have ability to remove active oxygen species, they are substantially ineffective to remove active oxygen species from the body. Accordingly, demand is mounting for drinks capable of efficiently removing active oxygen species from the body, which can be easily taken while playing sports.

Please replace paragraph [0013] at page 5 with the following amended paragraph:

[0013]

Further research has revealed that colloidal platinum particles in the colloidal platinum dispersion prepared by the method of JP 2001-79382 A have a wide particle size distribution, which largely differs from lot to lot. However, because large colloidal platinum particles are not absorbed in a human body through digestive organs, they fail to remove ~~active~~ <u>reactive</u> oxygen species in the body. Further, because a higher percentage of large colloidal platinum particles results in decrease in the total surface area of the colloidal platinum particles at the same platinum concentration, the ability of the colloidal platinum dispersion to remove active oxygen species is inevitably lowered. Also, if the particle size distribution largely differed from lot to lot, the percentage of large colloidal platinum particles having substantially no contribution to the removal of active oxygen species would be different even at the same platinum concentration, resulting in a varying percentage of effective colloidal platinum particles and thus extreme difference in the ability to remove ~~active~~ <u>reactive</u> oxygen species. Accordingly, the method of JP 2001-79382 A fails to produce a colloidal platinum dispersion having stably high ability to remove active oxygen species.

Please replace paragraph [0027] at page 8 with the following amended paragraph:

[0027]

The method of the present invention can stably produce a nanocolloidal platinum dispersion having a narrow particle size distribution. Because the nanocolloidal platinum dispersion contains substantially no large nanocolloidal platinum particles with their percentage only little changing, it stably has high ability to remove ~~active~~ <u>reactive</u> oxygen species. The method of the present invention can produce a dispersion containing nanocolloidal platinum and sodium polyacrylate. Because both of platinum and sodium polyacrylate are confirmed to be

safe as food additives, the nanocolloidal platinum dispersion containing sodium polyacrylate may be included in drinks.

Please replace paragraph [0033] at pages 10-11 with the following amended paragraph:

[0033]

The average particle size of the nanocolloidal platinum is 1-5 nm, preferably 1-3 nm, particularly 1.5-2.5 nm. 90% or more of the nanocolloidal platinum preferably has a particle size within a range of 0.1-10 nm, more preferably 1-3 nm. Because of such a narrow particle size distribution and an average particle size in a range of 1-5 nm, it is considered that the nanocolloidal platinum exhibits high ability to remove ~~active~~ reactive oxygen species when taken in a human body. The nanocolloidal platinum dispersion having such a narrow particle size distribution can be produced by a method described below.

Please replace paragraph [0034] at page 11 with the following amended paragraph:

[0034]

The nanocolloidal platinum has high ability to remove active oxygen species such as superoxide anion radicals, hydroxyl radicals, hydrogen peroxide, etc. The concentration IC_{50} of nanocolloidal platinum necessary for reducing ~~active~~ reactive oxygen species to half is preferably 200 mmol/L or less, more preferably 180 mmol/L or less. The IC_{50} is defined herein as the minimum concentration of the nanocolloidal platinum dispersion necessary for making a ratio of Cpt/Cw to 50%, wherein Cw represents the concentration of active oxygen species measured 45 seconds after water is added to an equal amount of an aqueous solution generating a predetermined concentration of active oxygen species, and Cpt represents the concentration of active oxygen species measured 45 seconds after the nanocolloidal platinum dispersion is mixed with an equal amount of the same aqueous solution generating active oxygen species. It is

presumed that the generated active oxygen species are mainly superoxide anion radicals. However, because other active oxygen species (hydroxyl radicals, hydrogen peroxide, etc.) can be removed, the concentration of ~~active~~ reactive oxygen species means the total concentration of all ~~active~~ reactive oxygen species. Because the concentration of ~~active~~ reactive oxygen species cannot directly be measured, it is determined from the measured amount of a captor of an ~~active~~ reactive oxygen species.

Please replace paragraph [0048] at pages 15-16 with the following amended paragraph:

[0048]

Using the same procedures as in the production method of the nanocolloidal platinum dispersion of the present invention, nanocolloidal dispersions of other precious metals than platinum can be produced. Producible nanocolloidal dispersions are, for instance, a nanocolloidal gold dispersion and a nanocolloidal platinum/gold dispersion. The nanocolloidal platinum/gold is nanocolloid consisting of platinum and gold. The nanocolloidal platinum/gold has a core-shell structure comprising (a) a platinum core and a gold shell, or (b) a platinum shell and a gold core. Because gold is also a permitted food additive like platinum, it may be taken safely. However, the nanocolloidal platinum has higher ability to remove ~~active~~ reactive oxygen species than the nanocolloidal gold and the nanocolloidal platinum/gold.

Please replace paragraph [0049] at page 16 with the following amended paragraph:

[0049]

Nanocolloidal precious metal dispersions containing other colloid-protecting agents than sodium polyacrylate may also be prepared. Usable colloid-protecting agents include methyl cellulose, cyclodextrin, polycyclodextrin and glutathione. Methyl cellulose is permitted under The Food Sanitation Act, and thus can be taken in a human body. Because dextrin and glutathione are components contained in usual food, they can be taken safely. Because these colloid-protecting agents are coordinated around platinum and/or gold to some extent, the affinity of platinum and/or gold for a solvent is improved. However, even if these protecting agents exist in the dispersion, the nanocolloid of precious metals would not be able to be sufficiently dispersed. Unless sodium polyacrylate is used, a nanocolloidal dispersion having excellent ability to remove ~~active~~ reactive oxygen species cannot be obtained. Accordingly, the nanocolloidal platinum dispersion comprising nanocolloidal platinum and sodium polyacrylate is optimum for the removal of ~~active~~ reactive oxygen.

Please replace paragraph [0058] at page 19 with the following amended paragraph:

[0058]

Various vitamins may be used, regardless of whether they are water-soluble or lipophilic. Their examples include retinol palmitate, bisbentiamine, riboflavin, pyridoxine hydrochloride, cyanocobalamine, sodium ascorbate, cholecalciferol, nicotinamide, calcium pantothenate, folic acid, biotin, and choline bitartrate. Among them, vitamin E and/or vitamin C are preferably added. Vitamin E and/or vitamin C exhibit high ability to remove ~~active~~ reactive oxygen species immediately after ingestion. It is thus expected that the drinks containing vitamin E and/or vitamin C exhibit improved ability to remove ~~active~~ reactive oxygen species immediately after ingestion.

Please replace paragraph [0063] at page 21 with the following amended paragraph:

[0063]

How much nanocolloidal platinum-containing drink should be taken depends on the age of a person having the drink, the purpose of having the drink, the concentration of nanocolloidal platinum, etc. When a usually active adult person takes about 1-100 mL/kg/day of the drink having a nanocolloidal platinum concentration of about 0.1 mmol/L, ~~active~~ reactive oxygen species are extremely effectively removed from his or her body.

Please replace paragraph [0068] at pages 22-23 with the following amended paragraph:

[0068]

(2) Measurement of antioxidant ability

(a) Hypoxanthine (HXN) / xanthine oxidase (XOD)

(i) Measurement of amount of ~~active~~ reactive oxygen species captor

Using HXN as a reaction substrate and XOD as an oxidizing enzyme, ~~active~~ reactive oxygen species (simply expressed by $O_2^{-}\cdot$) were generated by an enzymatic reaction, to cause a reaction with the aqueous PAA-Pt dispersion as described below. First, 1 mmol/L of the aqueous PAA-Pt dispersion prepared in the above step (1) was diluted by Milli-Q water to 25 mmol/L, 50 mmol/L, 75 mmol/L, 100 mmol/L, 125 mmol/L, 150 mmol/L and 200 mmol/L, respectively. Dissolved in 100 mL of each diluted dispersion were 50 mL of an aqueous HXN solution [5.5 mmol/L, containing 200 mmol/L of a phosphoric acid buffer (pH 7.5), HXN: available from Wako Pure Chemical Industries, Ltd.], and 15 mL of 5,5-dimethyl-1-pyrroline-N-oxide (DMPO, available from Dojindo Laboratories). 50 mL of an XOD solution [0.2 U/mL, containing 200 mmol/L of a phosphoric acid buffer (pH 7.5), XOD: available from Roche] was added to the resultant aqueous dispersion of HXN and PAA-Pt containing DMPO, to form an

aqueous HXN-PAA-Pt-XOD dispersion containing DMPO. To prevent the deactivation of XOD, the XOD-containing solution was cooled in an ice bath.

Please replace paragraph [0078] at pages 25-26 with the following amended paragraph:

[0078]

(d) Measurement of change with time of ability to remove active oxygen species

To evaluate the change with time of the ability of PAA-Pt to remove ~~active~~ reactive oxygen species in the NADPH-PMS system, DMPO was added to the aqueous NADPH-PAA-Pt-PMS dispersion after 0 minutes, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes and 60 minutes, respectively, from the addition of PMS, and the amount of DMPO-OOH in the aqueous dispersion was measured using ESR after 45 seconds from the addition of DMPO. The other conditions than the above were the same as in the above step (b). The percentage of $O_2^{-\cdot}$ remaining in the aqueous dispersion was determined from the measured amount of an $O_2^{-\cdot}$captor formed. The change with time of the percentage of the remaining $O_2^{-\cdot}$ after the addition of PMS in the preparation of the aqueous NADPH-PAA-Pt-PMS dispersion is shown by white circles in Fig. 2.

Please replace paragraph [0086] at pages 29-30 with the following amended paragraph:

[0086]

Comparative Example 3

The IC50 of SOD was determined in the same manner as in the step (2)(a) in Example 1, except for adding an aqueous solution of SOD (antioxidant enzyme, WK-013 available from Wakamoto Pharmaceutical Co., Ltd.) to an aqueous HXN/XOD solution generating O2-·. The results are shown in Table 2.

Table 2

No.	Material for Removing ~~Active~~ Reactive Oxygen	IC_{50} ± S.D.* (μmol/L)
Comparative Example 2	Vitamin C	27.5 ± 2.3
Comparative Example 3	SOD	$(1.1 \pm 0.2) \times 10^{-4}$
Example 1	PAA-Pt	135.7 ± 9.0

Note: * "S.D." means a standard deviation.

Please replace paragraph [0096] at page 33 with the following amended paragraph:

[0096]

However, Reference Example 1 indicates that all having low oxidation-reduction potential do not necessarily have large ability to remove ~~active~~ reactive oxygen species. Namely, the PVP-Pt of Reference Example 1 has as small IC_{50} as 148.7 ± 23.2 mmol/L despite as high oxidation-reduction potential as 629 ± 0.9 mV, while "Hakkin-Gensui" of Comparative Example 4 has as large IC_{50} as 251.4 ± 7.4 mmol/L despite its oxidation-reduction potential of 470 ± 2.3 mV lower than that of the PVP-Pt of Reference Example 1.

Please replace paragraph [0097] at page 33 with the following amended paragraph:

[0097]

Reference Example 2

The influence of a protecting agent on the oxidation-reduction potential of the nanocolloidal platinum was examined as follows. Sodium polyacrylate (PAA), a protecting agent for PAA-Pt, polyvinylpyrrolidone (PVP), a protecting agent for PVP-Pt, and Polysolvate 80, a protecting agent for "Hakkin-Gensui" were measured with respect to oxidation-reduction potential. The results are shown in Table 4.

Table 4

Protecting Agent	Oxidation-Reduction Potential ± Standard Deviation (mV)
PAA	238 ± 2.1
PVP	348 ± 1.2
~~polysolvate~~ Polysorbate 80	280 ± 1.3